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PMID: 15108807 [PubMed - indexed for MEDLINE]

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L2 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:847609 CAPLUS
DN 141:308676
TI TGF-β activated kinase 1 (TAK1)-mediated regulation of SMAD activity and therapeutic use for inhibition of osteogenesis
IN Gazit, Dan; Pelled, Gadi; Turgeman, Gadi; Hoffmann, Andrea; Gross, Gerhard; Wodarczyk, Claas; Verschueren, Kristin
PA Yissum Research Development Company of the Hebrew University of Jerusalem, Israel; Gesellschaft Fur Biotechnologische Forschung Gbf; Flanders Interuniversity for Biotechnology Vzw Vib; K.U. Leuven Research & Development
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004087862	A2	20041014	WO 2004-IL286	20040329

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2003-458954P P 20030401
AB This invention is directed to methods, nucleic acids and compns. in TAK1-mediated regulation of SMAD activity. Promotion of TAK1 interaction with MH2 domains in SMADs neg. regulates SMAD biol. activity. BMP-mediated SMAD activity is subject to TAK1 effects.

L2 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:360779 CAPLUS
DN 138:380400
TI TAK1-TAB1 fusion protein: a novel constitutively active mitogen-activated protein kinase kinase kinase for use in drug screening
IN Sugita, Naohisa; Sakurai, Hiroaki; Sato, Naoya
PA Tanabe Seiyaku Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 34 pp.

CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2003135070	A2	20030513	JP 2001-335988	20011101
PRAI	JP 2001-335988		20011101		

AB A fusion protein comprising human transforming growth factor-β-activated kinase 1 (TAK1) N-terminal MAPKKK domain and human TAK1 binding protein 1 (TAB1) C-terminal TAK1 activation domain, functional as active mutant TAK1, encoding cDNAs, recombinant expression, and use in screening TAK1 inhibitors, are disclosed. TAK1 and TAB1 are connect via a linker peptide. Activation of JNK, p38, or IKK, or induction of cytokine production, such as IL-6, IL-1, or TNF, may be assayed for screening. TAK1 mitogen-activated protein kinase kinase kinase (MAP3K) is activated by its specific activator, TAK1-binding protein 1 (TAB1). A constitutively active TAK1 mutant has not yet been generated due to the indispensable requirement of TAB1 for TAK1 kinase activity. In this study, the authors generated a novel constitutively active TAK1 by fusing its kinase domain to the minimal TAK1-activation domain of TAB1. Co-immunopptn. assay demonstrated that these domains interacted intra-molecularly. The TAK1-TAB1 fusion protein showed a significant MAP3K activity in vitro and activated c-Jun N-terminal kinase/p38 MAPKs and IκB kinase in vivo, which was followed by increased production of interleukin-6. These results indicate that the fusion protein is useful for characterizing the physiol. roles of the TAK1-TAB1 complex.

L2 ANSWER 3 OF 16 MEDLINE on STN DUPLICATE 1
AN 2003165469 MEDLINE
DN PubMed ID: 12556533
TI Regulation of the interleukin-1-induced signaling pathways by a novel member of the protein phosphatase 2C family (PP2Cepsilon).
AU Li Ming Guang; Katsura Koji; Nomiyama Hisayuki; Komaki Ken-Ichiro; Ninomiya-Tsuji Jun; Matsumoto Kunihiro; Kobayashi Takayasu; Tamura Shinri
CS Department of Biochemistry, Institute of Development, Aging, and Cancer, Tohoku University, 4-1 Seiryomachi, Aoba-ku, Sendai 980-8575, Japan.
SO Journal of biological chemistry, (2003 Apr 4) 278 (14) 12013-21.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AY184801
EM 200305
ED Entered STN: 20030410
Last Updated on STN: 20030520
Entered Medline: 20030519
AB Although TAK1 signaling plays essential roles in eliciting cellular responses to interleukin-1 (IL-1), a proinflammatory **cytokine**, how the IL-1-**TAK1** signaling pathway is positively and negatively regulated remains poorly understood. In this study, we investigated the possible role of a novel protein phosphatase 2C (PP2C) family member, PP2Cepsilon, in the regulation of the IL-1-TAK1 signaling pathway. PP2Cepsilon was composed of 303 amino acids, and the overall similarity of amino acid sequence between PP2Cepsilon and PP2Calpha was found to be 26%. Ectopic expression of PP2Cepsilon inhibited the IL-1- and TAK1-induced activation of mitogen-activated protein kinase kinase 4 (MKK4)-c-Jun N-terminal kinase or MKK3-p38 signaling pathway. PP2Cepsilon dephosphorylated TAK1 in vitro. Co-immunoprecipitation experiments indicated that PP2Cepsilon associates stably with TAK1 and attenuates the binding of TAK1 to MKK4 or MKK6. Ectopic expression of a phosphatase-negative mutant of PP2Cepsilon, PP2Cepsilon(D/A), which acted as a dominant negative form, enhanced both the association between TAK1

and MKK4 or MKK6 and the TAK1-induced activation of an AP-1 reporter gene. The association between PP2Cepsilon and TAK1 was transiently suppressed by IL-1 treatment of the cells. Taken together, these results suggest that, in the absence of IL-1-induced signal, PP2Cepsilon contributes to keeping the TAK1 signaling pathway in an inactive state by associating with and dephosphorylating TAK1.

L2 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:883731 CAPLUS
DN 139:394860
TI Feedback control of the protein kinase TAK1 by SAPK2a/p38α
AU Cheung, Peter C. F.; Campbell, David G.; Nebreda, Angel R.; Cohen, Philip
CS MSI/WTB Complex, School of Life Sciences, MRC Protein Phosphorylation Unit, University of Dundee, Dundee, DD1 5EH, UK
SO EMBO Journal (2003), 22(21), 5793-5805
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB TAB1, a subunit of the kinase TAK1, was phosphorylated by SAPK2a/p38α at Ser423, Thr431 and Ser438 in vitro. TAB1 became phosphorylated at all three sites when cells were exposed to cellular stresses, or stimulated with tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) or lipopolysaccharide (LPS). The phosphorylation of Ser423 and Thr431 was prevented if cells were pre-incubated with SB 203580, while the phosphorylation of Ser438 was partially inhibited by PD 184352. Ser423 is the first residue phosphorylated by SAPK2a/p38α that is not followed by proline. The activation of TAK1 was enhanced by SB 203580 in LPS-stimulated macrophages, and by proinflammatory cytokines or osmotic shock in epithelial KB cells or embryonic fibroblasts. The activation of TAK1 by TNF-α, IL-1 or osmotic shock was also enhanced in embryonic fibroblasts from SAPK2a/p38α-deficient mice, while incubation of these cells with SB 203580 had no effect. Our results suggest that TAB1 participates in a SAPK2a/p38α-mediated feedback control of TAK1, which not only limits the activation of SAPK2a/p38α but synchronizes its activity with other signalling pathways that lie downstream of TAK1 (JNK and IKK).
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 16 MEDLINE on STN DUPLICATE 2
AN 2003429388 MEDLINE
DN PubMed ID: 12969270
TI TAK1-mediated induction of nitric oxide synthase gene expression in glial cells.
AU Bhat Narayan R; Shen Qin; Fan Fan
CS Department of Neurology, Medical University of South Carolina, Charleston, South Carolina 29425, USA.. bhatnr@musc.edu
NC NS41035 (NINDS)
SO Journal of neurochemistry, (2003 Oct) 87 (1) 238-47.
Journal code: 2985190R. ISSN: 0022-3042.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200311
ED Entered STN: 20030913
Last Updated on STN: 20031113
Entered Medline: 20031112
AB Inflammatory cell signaling leading to transcriptional activation is primarily mediated by signal transduction via mitogen-activated protein kinase (MAPK) and NFkappaB pathways. A common upstream kinase that signals the activation of these pathways is TGFbeta-activated kinase 1 (**TAK1**), which itself becomes activated in response to

cytokines and upon engagement of a class of cell surface receptors involved in innate immunity, that is Toll-like receptors (TLRs) by bacterial and viral pathogens. This study directly tests the role of TAK1 in the induction of inducible nitric oxide (NO) synthase (iNOS) in glial cells, which represent immune-regulatory cells of the CNS, by transient transfection assays. Transfection of C-6 glia, primary astrocytes and a rat microglial cell line with TAK1 (but not its inactive form) along with its activator protein, TAK1-binding protein 1 (TAB1) resulted in a marked stimulation of a co-transfected rat iNOS promoter-reporter construct (iNOS-Luc). TAK1-induced iNOS-Luc activity was substantially inhibited by pharmacological inhibitors of the known downstream kinases, p38 MAPK and JNK (SB203580 and SP620125), and was almost completely blocked by co-expression of a phosphorylation mutant of IkappaB. TAK1/TAB1 also induced the production of NO and the expression of iNOS in microglial cells in a p38 MAPK-, JNK- and NFkappaB-dependent manner. The results of these studies provide evidence for an important role for TAK1-mediated intracellular signaling, via p38 MAPK, JNK and NFkappaB, in the transcriptional activation of iNOS in glial cells.

L2 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 3
AN 2003132605 MEDLINE
DN PubMed ID: 12598905
TI **Cytokines** suppress adipogenesis and PPAR-gamma function through the **TAK1**/TAB1/NIK cascade.
AU Suzawa Miyuki; Takada Ichiro; Yanagisawa Junn; Ohtake Fumiaki; Ogawa Satoko; Yamauchi Toshimasa; Kadowaki Takashi; Takeuchi Yasuhiro; Shibuya Hiroshi; Gotoh Yukiko; Matsumoto Kunihiro; Kato Shigeaki
CS Institute of Molecular and Cellular Biosciences, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan.
SO Nature cell biology, (2003 Mar) 5 (3) 224-30.
Journal code: 100890575. ISSN: 1465-7392.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030321
Last Updated on STN: 20030422
Entered Medline: 20030421
AB Pluripotent mesenchymal stem cells in bone marrow differentiate into adipocytes, osteoblasts and other cells. Balanced cytodifferentiation of stem cells is essential for the formation and maintenance of bone marrow; however, the mechanisms that control this balance remain largely unknown. Whereas cytokines such as interleukin-1 (IL-1) and tumour-necrosis factor-alpha (TNF-alpha) inhibit adipogenesis, the ligand-induced transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-gamma), is a key inducer of adipogenesis. Therefore, regulatory coupling between cytokine- and PPAR-gamma-mediated signals might occur during adipogenesis. Here we show that the ligand-induced transactivation function of PPAR-gamma is suppressed by IL-1 and TNF-alpha, and that this suppression is mediated through NF-kappaB activated by the TAK1/TAB1/NF-kappaB-inducing kinase (NIK) cascade, a downstream cascade associated with IL-1 and TNF-alpha signalling. Unlike suppression of the PPAR-gamma transactivation function by mitogen-activated protein kinase-induced growth factor signalling through phosphorylation of the A/B domain, NF-kappaB blocks PPAR-gamma binding to DNA by forming a complex with PPAR-gamma and its AF-1-specific co-activator PGC-2. Our results suggest that expression of IL-1 and TNF-alpha in bone marrow may alter the fate of pluripotent mesenchymal stem cells, directing cellular differentiation towards osteoblasts rather than adipocytes by suppressing PPAR-gamma function through NF-kappaB activated by the TAK1/TAB1/NIK cascade.

L2 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 4

AN 2003040238 MEDLINE
DN PubMed ID: 12547194
TI TAK1 is critical for IkappaB kinase-mediated activation of the NF-kappaB pathway.
AU Takaesu Giichi; Surabhi Rama M; Park Kyu-Jin; Ninomiya-Tsuji Jun; Matsumoto Kunihiro; Gaynor Richard B
CS Division of Hematology-Oncology, Department of Medicine, Harold Simmons Cancer Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8594, USA.
SO Journal of molecular biology, (2003 Feb 7) 326 (1) 105-15.
Journal code: 2985088R. ISSN: 0022-2836.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030128
Last Updated on STN: 20030311
Entered Medline: 20030310
AB Cytokine treatment stimulates the IkappaB kinases, IKKalpha and IKKbeta, which phosphorylate the IkappaB proteins, leading to their degradation and activation of NF-kappaB regulated genes. A clear definition of the specific roles of IKKalpha and IKKbeta in activating the NF-kappaB pathway and the upstream kinases that regulate IKK activity remain to be elucidated. Here, we utilized small interfering RNAs (siRNAs) directed against IKKalpha, IKKbeta and the upstream regulatory kinase **TAK1** in order to better define their roles in **cytokine**-induced activation of the NF-kappaB pathway. In contrast to previous results with mouse embryo fibroblasts lacking either IKKalpha or IKKbeta, which indicated that only IKKbeta is involved in cytokine-induced NF-kappaB activation, we found that both IKKalpha and IKKbeta were important in activating the NF-kappaB pathway. Furthermore, we found that the MAP3K TAK1, which has been implicated in IL-1-induced activation of the NF-kappaB pathway, was also critical for TNFalpha-induced activation of the NF-kappaB pathway. TNFalpha activation of the NF-kappaB pathway is associated with the inducible binding of TAK1 to TRAF2 and both IKKalpha and IKKbeta. This analysis further defines the distinct in vivo roles of IKKalpha, IKKbeta and **TAK1** in **cytokine**-induced activation of the NF-kappaB pathway.

L2 ANSWER 8 OF 16 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2004:193972 BIOSIS
DN PREV200400194532
TI **TAK1** - mediated induction of nitric oxide synthase and **cytokine** gene expression in glial cells.
AU White, S. [Reprint Author]; Shen, Q. [Reprint Author]; Fan, F. [Reprint Author]; Griesemer, D. [Reprint Author]; Bhat, N. R. [Reprint Author]
CS Neurol., Med. Univ. of South Carolina, Charleston, SC, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 103.12. http://sfn.scholarone.com. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004
AB Inflammatory cell signaling leading to transcriptional activation is primarily mediated by signal transduction via mitogen-activated protein kinase (MAPK) and NFKAPPAB pathways. A common upstream kinase that signals the activation of these pathways is TGFbeta-activated kinase1 (**TAK1**), which itself becomes activated in response to **cytokines** and upon engagement of a class of cell surface receptors

involved in innate immunity i.e., Toll-like receptors (TLRs) by bacterial and viral pathogens. This study directly tests the role of TAK1 in the induction of inducible nitric oxide (NO) synthase (iNOS) and cytokines in glial cells, the immune-regulatory cells of the CNS, by transient transfection assays. Transfection of C-6 glia and a rat microglial cell line with TAK1 (but not its inactive form) along with its activator protein i.e., TAK1-binding protein 1 (TAB1) resulted in a marked stimulation of a co-transfected rat iNOS promoter-reporter construct (iNOS-Luc). TAK1-induced iNOS-Luc activity was substantially inhibited by pharmacological inhibitors of the known down-stream kinases i.e., p38 MAPK and JNK (i.e., SB203580 and SP620125) and was almost completely blocked by co-expression of a phosphorylation mutant of IKAPPAB. TAK1/TAB1 also induced the production of NO and the expression of iNOS and the cytokine i.e., IL-1beta in microglial cells in a p38 MAPK-, JNK-and NFKAPPAB-dependent manner. The results of these studies provide evidence for an important role for TAK1-mediated intracellular signaling, via p38 MAPK, JNK and NFKAPPAB, in the transcriptional activation of iNOS and cytokine genes in glial cells.

L2 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:619468 CAPLUS
DN 137:349704
TI TAK1-dependent activation of AP-1 and c-Jun N-terminal kinase by receptor activator of NF-κB
AU Lee, Soo Woong; Han, Sang-In; Kim, Hong-Hee; Lee, Zang Hee
CS Research Center for Proteineous Materials, School of Dentistry, Chosun University, Gwangju, S. Korea
SO Journal of Biochemistry and Molecular Biology (2002), 35(4), 371-376
CODEN: JBMBE5; ISSN: 1225-8687
PB Springer-Verlag Singapore Pte. Ltd.
DT Journal
LA English
AB The receptor activator of nuclear factor kappa B (RANK) is a member of the tumor necrosis factor (TNF) receptor superfamily. It plays a critical role in osteoclast differentiation, lymph node organogenesis, and mammary gland development. The stimulation of RANK causes the activation of transcription factors NF-κB and activator protein 1 (AP1), and the mitogen activated protein kinase (MAPK) c-Jun N-terminal kinase (JNK). In the signal transduction of RANK, the recruitment of the adaptor mols., TNF receptor-associated factors (TRAFs), is an initial cytoplasmic event. Recently, the association of the MAPK kinase kinase, transforming growth factor-β-activated kinase 1 (TAK1), with TRAF6 was shown to mediate the IL-1 signaling to NF-κB and JNK. We investigated whether or not TAK1 plays a role in RANK signaling. A dominant-neg. form of TAK1 was discovered to abolish the RANK-induced activation of AP1 and JNK. The AP1 activation by TRAF2, TRAF5, and TRAF6 was also greatly suppressed by the dominant-neg. TAK1. The inhibitory effect of the TAK1 mutant on RANK- and TRAF-induced NF-κB activation was also observed, but less efficiently. Our findings indicate that TAK1 is involved in the MAPK cascade and NF-κB pathway that is activated by RANK.
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:141670 CAPLUS
DN 139:5173
TI Molecular mechanisms of the TRAF6-mediated cytokine signaling
AU Inoue, Jun-ichiro
CS Division of cellular and molecular biology, Department of Cancer Biology, Institute of Medical Science, University of Tokyo, Japan
SO Molecular Medicine (Tokyo, Japan) (2002), 39(Rinji Zokango, Men'eki 2003), 62-71
CODEN: MOLMEL; ISSN: 0918-6557
PB Nakayama Shoten

DT Journal; General Review
LA Japanese
AB A review discusses role of TRAF6 in signaling of cytokines through MAP kinase, RANK, and NF-κB mols.

L2 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 5
AN 2001441648 MEDLINE
DN PubMed ID: 11397816
TI Involvement of Hgs/Hrs in signaling for **cytokine**-mediated c-fos induction through interaction with **TAK1** and Pak1.
AU Sasaki Y; Sugamura K
CS Department of Microbiology and Immunology, Tohoku University Graduate School of Medicine and CREST Program of the Japan Science, and Technology Corporation, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan.
SO Journal of biological chemistry, (2001 Aug 10) 276 (32) 29943-52.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200109
ED Entered STN: 20010813
Last Updated on STN: 20030105
Entered Medline: 20010906
AB Hgs/Hrs is a tyrosine-phosphorylated FYVE finger protein that is induced by stimulation with various cytokines and growth factors. Here we show that Hgs plays critical roles in the signaling pathway for the interleukin-2-induced activation of the serum-response element and cyclic AMP-response element of the c-fos promoter. We found that Hgs associated physically with transforming growth factor-beta-activated kinase 1 (TAK1) and p21-activated kinase 1 (Pak1), which mediate the activation of c-Jun N-terminal kinase and serum response factor, respectively, leading to transactivation via the serum-response element and cyclic AMP-response element. These results suggest that Hgs is involved in the TAK1-JNK and Pak1-serum response factor pathways for the c-fos induction that is initiated by cytokines.

L2 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:761049 CAPLUS
DN 136:52546
TI Raf kinase inhibitor protein interacts with NF-κB-inducing kinase and TAK1 and inhibits NF-κB activation
AU Yeung, Kam C.; Rose, David W.; Dhillon, Amardeep S.; Yaros, Diane; Gustafsson, Marcus; Chatterjee, Devasis; McFerran, Brian; Wyche, James; Kolch, Walter; Sedivy, John M.
CS Department of Molecular Biology, Cell Biology, Brown University, Providence, RI, 02912, USA
SO Molecular and Cellular Biology (2001), 21(21), 7207-7217
CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English
AB The Raf kinase inhibitor protein (RKIP) acts as a neg. regulator of the mitogen-activated protein (MAP) kinase (MAPK) cascade initiated by Raf-1. RKIP inhibits the phosphorylation of MAP/extracellular signal-regulated kinase 1 (MEK1) by Raf-1 by disrupting the interaction between these two kinases. The authors show here that RKIP also antagonizes the signal transduction pathways that mediate the activation of the transcription factor nuclear factor kappa B (NF-κB) in response to stimulation with tumor necrosis factor α (TNF-α) or interleukin 1β. Modulation of RKIP expression levels affected NF-κB signaling independent of the MAPK pathway. Genetic epistasis anal. involving the ectopic expression of kinases acting in the NF-κB pathway indicated that RKIP acts upstream of the kinase complex that mediates the

phosphorylation and inactivation of the inhibitor of NF-κB (IκB). In vitro kinase assays showed that RKIP antagonizes the activation of the IκB kinase (IKK) activity elicited by TNF-α. RKIP phys. interacted with 4 kinases of the NF-κB activation pathway, NF-κB-inducing kinase, transforming growth factor β-activated kinase 1 (TAK1), IKKα, and IKKβ. This mode of action bears striking similarities to the interactions of RKIP with Raf-1 and MEK1 in the MAPK pathway. Emerging data from diverse organisms suggest that RKIP and RKIP-related proteins represent a new and evolutionarily highly conserved family of protein kinase regulators. Since the MAPK and NF-κB pathways have physiol. distinct roles, the function of RKIP may be, in part, to coordinate the regulation of these pathways.

RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 16 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:4979 BIOSIS
DN PREV200200004979
TI Inhibition of adipogenesis by **cytokines** with suppression of PPARgamma function through **TAK1**/TAB1-NIK promotes osteoblastogenesis.
AU Suzawa, M. [Reprint author]; Takada, I. [Reprint author]; Yanagisawa, J. [Reprint author]; Takeuchi, Y.; Goroh, Y. [Reprint author]; Matsumoto, K.; Kato, S. [Reprint author]
CS IMBC, University of Tokyo/CREST, Tokyo, Japan
SO Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S496. print.
Meeting Info.: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research. Phoenix, Arizona, USA. October 12-16, 2001.
CODEN: JBMREJ. ISSN: 0884-0431.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 28 Dec 2001
Last Updated on STN: 25 Feb 2002

L2 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:278128 CAPLUS
DN 132:320956
TI Method for screening compound inhibiting signal transduction of inflammatory cytokine
IN Tsuchiya, Masayuki; Ohtomo, Toshihiko; Sugamata, Yasuhiro; Matsumoto, Kunihiro
PA Chugai Seiyaku K. K., Japan
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000023610	A1	20000427	WO 1999-JP5817	19991021
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9962278	A1	20000508	AU 1999-62278	19991021

EP 1127944 A1 20010829 EP 1999-949347 19991021
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRAI JP 1998-299962 A 19981021
WO 1999-JP5817 W 19991021
AB By inhibiting the signal transduction of **TAK1**, effects of inflammatory **cytokines** are depressed, the production of inflammatory cytokines (IL-1, TNF, etc.) induced by inflammatory stimulus is depressed and the production of other inflammatory cytokines (IL-6, etc.) induced by the inflammatory cytokines is depressed. The assay comprises contacting TAK1 and TAB1 (TAK1 kinase binding protein 1) with the sample, monitoring formation of TAK1 kinase-TAB1 complexes, and screening compound that inhibits TAK1-TAB1 binding. The method may also use labeled anti-TAB1 antibody for drug screening.
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 6
AN 2000420860 MEDLINE
DN PubMed ID: 10781614
TI p38 MAPK and NF-kappa B collaborate to induce interleukin-6 gene expression and release. Evidence for a cytoprotective autocrine signaling pathway in a cardiac myocyte model system.
AU Craig R; Larkin A; Mingo A M; Thuerauf D J; Andrews C; McDonough P M; Glembotski C C
CS SDSU Heart Institute and The Department of Biology, San Diego State University, San Diego, California 92182, USA.
NC HL 56861 (NHLBI)
HL-46345 (NHLBI)
NS/HL-25073 (NINDS)
+
SO Journal of biological chemistry, (2000 Aug 4) 275 (31) 23814-24.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000915
Last Updated on STN: 20020420
Entered Medline: 20000907
AB In cardiac myocytes, the stimulation of p38 MAPK by the MAPKK, MKK6, activates the transcription factor, NF-kappaB, and protects cells from apoptosis. In the present study in primary neonatal rat cardiac myocytes, constitutively active MKK6, MKK6(Glu), bound to IkappaB kinase (IKK)-beta and stimulated its abilities to phosphorylate IkappaB and to activate NF-kappaB. MKK6(Glu) induced NF-kappaB-dependent interleukin (IL)-6 transcription and IL-6 release in a p38-dependent manner. IL-6 protected myocardial cells against apoptosis. Like IL-6, TNF-alpha, which activates both NF-kappaB and p38, also induced p38-dependent IL-6 expression and release and protected myocytes from apoptotis. While TNF-alpha was relatively ineffective, IL-6 activated myocardial cell STAT3 by about 8-fold, indicating a probable role for this transcription factor in IL-6-mediated protection from apoptosis. TNF-alpha-mediated IL-6 induction was inhibited by a kinase-inactive form of the MAPKKK, TGF-beta activated protein kinase (Tak1), which is known to activate p38 and NF-kappaB in other cell types. Thus, by stimulating both p38 and NF-kappaB, **Tak1**-activating **cytokines**, like TNF-alpha, can induce IL-6 expression and release. Moreover, the myocyte-derived IL-6 may then function in an autocrine and/or paracrine fashion to augment myocardial cell survival during stresses that activate p38.

L2 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 7
AN 2000148839 MEDLINE

DN PubMed ID: 10683140
TI Cross-regulation of the Wnt signalling pathway: a role of MAP kinases.
AU Behrens J
CS Max-Delbruck-Center for Molecular Medicine, Robert-Rossle-Str. 10, Germany.. jbehren@mdc-berlin.de
SO Journal of cell science, (2000 Mar) 113 (Pt 6) 911-9.
Journal code: 0052457. ISSN: 0021-9533.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000531
AB The Wnt signal transduction pathway regulates various aspects of embryonal development and is involved in cancer formation. Wnts induce the stabilisation of cytosolic (beta)-catenin, which then associates with TCF transcription factors to regulate expression of Wnt-target genes. At various levels the Wnt pathway is subject to cross-regulation by other components. Recent evidence suggests that a specific MAP kinase pathway involving the MAP kinase kinase kinase TAK1 and the MAP kinase NLK counteract Wnt signalling. In particular, homologues of TAK1 and NLK, MOM-4 and LIT-1, negatively regulate Wnt-controlled cell fate decision in the early Caenorhabditis elegans embryo. Moreover, TAK1 activates NLK, which phosphorylates TCFs bound to (beta)-catenin. This blocks nuclear localization and DNA binding of TCFs. Since **TAK1** is activated by TGF-(beta) and various **cytokines**, it might provide an entry point for regulation of the Wnt system by other pathways. In addition, alterations in TAK1-NLK might play a role in cancer.

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=> S (TAK1) (8A) (IL-1 or IL-6 or TNF)
L3          81 (TAK1) (8A) (IL-1 OR IL-6 OR TNF)

=> s (IL-1 or IL-6 or TNF) (3A) (production or expression)
L4       75257 (IL-1 OR IL-6 OR TNF) (3A) (PRODUCTION OR EXPRESSION)

=> s L4 (8A) TAK1
L5           9 L4 (8A) TAK1

=> duplicate
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
ENTER L# LIST OR (END):l5
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS, CAPLUS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L5
L6            3 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)

=> d l6 1-3 bib ab

L6   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:278128  CAPLUS
DN   132:320956
TI   Method for screening compound inhibiting signal transduction of
     inflammatory cytokine
IN   Tsuchiya, Masayuki; Ohtomo, Toshihiko; Sugamata, Yasuhiro; Matsumoto,
     Kunihiro
PA   Chugai Seiyaku K. K., Japan
SO   PCT Int. Appl., 100 pp.
     CODEN: PIXXD2
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   WO 2000023610         A1    20000427    WO 1999-JP5817          19991021
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
             MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
             SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9962278             A1    20000508    AU 1999-62278           19991021
     EP 1127944             A1    20010829    EP 1999-949347          19991021
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRAI JP 1998-299962        A     19981021
     WO 1999-JP5817        W     19991021
AB   By inhibiting the signal transduction of TAK1, effects of
     inflammatory cytokines are depressed, the prodn. of inflammatory
     cytokines (IL-1, TNF, etc.) induced by inflammatory
     stimulus is depressed and the production of other inflammatory cytokines
     (IL-6, etc.) induced by the inflammatory cytokines is depressed.  The
     assay comprises contacting TAK1 and TAB1 (TAK1 kinase binding protein 1)
     with the sample, monitoring formation of TAK1 kinase-TAB1 complexes, and
     screening compound that inhibits TAK1-TAB1 binding.  The method may also use
     labeled anti-TAB1 antibody for drug screening.
RE.CNT  19    THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 3     MEDLINE on STN                    DUPLICATE 1
```

AN 2000420860 MEDLINE
DN PubMed ID: 10781614
TI p38 MAPK and NF-kappa B collaborate to induce interleukin-6 gene expression and release. Evidence for a cytoprotective autocrine signaling pathway in a cardiac myocyte model system.
AU Craig R; Larkin A; Mingo A M; Thuerauf D J; Andrews C; McDonough P M; Glembotski C C
CS SDSU Heart Institute and The Department of Biology, San Diego State University, San Diego, California 92182, USA.
NC HL 56861 (NHLBI)
HL-46345 (NHLBI)
NS/HL-25073 (NINDS)
+
SO Journal of biological chemistry, (2000 Aug 4) 275 (31) 23814-24.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000915
Last Updated on STN: 20020420
Entered Medline: 20000907
AB In cardiac myocytes, the stimulation of p38 MAPK by the MAPKK, MKK6, activates the transcription factor, NF-kappaB, and protects cells from apoptosis. In the present study in primary neonatal rat cardiac myocytes, constitutively active MKK6, MKK6(Glu), bound to IkappaB kinase (IKK)-beta and stimulated its abilities to phosphorylate IkappaB and to activate NF-kappaB. MKK6(Glu) induced NF-kappaB-dependent interleukin (IL)-6 transcription and IL-6 release in a p38-dependent manner. IL-6 protected myocardial cells against apoptosis. Like IL-6, TNF-alpha, which activates both NF-kappaB and p38, also induced p38-dependent IL-6 expression and release and protected myocytes from apoptotis. While TNF-alpha was relatively ineffective, IL-6 activated myocardial cell STAT3 by about 8-fold, indicating a probable role for this transcription factor in IL-6-mediated protection from apoptosis. TNF-alpha-mediated IL-6 induction was inhibited by a kinase-inactive form of the MAPKKK, TGF-beta activated protein kinase (Tak1), which is known to activate p38 and NF-kappaB in other cell types. Thus, by stimulating both p38 and NF-kappaB, **Tak1**-activating cytokines, like TNF-alpha, can induce **IL-6 expression** and release. Moreover, the myocyte-derived IL-6 may then function in an autocrine and/or paracrine fashion to augment myocardial cell survival during stresses that activate p38.

L6 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 2
AN 2000167218 MEDLINE
DN PubMed ID: 10702308
TI TAK1 mitogen-activated protein kinase kinase kinase is activated by autophosphorylation within its activation loop.
AU Kishimoto K; Matsumoto K; Ninomiya-Tsuji J
CS Department of Molecular Biology, Graduate School of Science, Nagoya University and CREST, Japan Science and Technology Corporation, Chikusa-ku, Nagoya 464-8602, Japan.
SO Journal of biological chemistry, (2000 Mar 10) 275 (10) 7359-64.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB TAK1, a member of the mitogen-activated kinase kinase kinase family, is activated in vivo by various cytokines, including interleukin-1 (IL-1), or when ectopically expressed together with the TAK1-binding protein TAB1. However, this molecular mechanism of activation is not yet understood. We show here that endogenous TAK1 is constitutively associated with TAB1 and phosphorylated following IL-1 stimulation. Furthermore, TAK1 is constitutively phosphorylated when ectopically overexpressed with TAB1. In both cases, dephosphorylation of TAK1 renders it inactive, but it can be reactivated by preincubation with ATP. A mutant of TAK1 that lacks kinase activity is not phosphorylated either following IL-1 treatment or when coexpressed with TAB1, indicating that TAK1 phosphorylation is due to autophosphorylation. Furthermore, mutation to alanine of a conserved serine residue (Ser-192) in the activation loop between kinase domains VII and VIII abolishes both phosphorylation and activation of TAK1. These results suggest that **IL-1** and ectopic **expression** of TAB1 both activate **TAK1** via autophosphorylation of Ser-192.

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